BIOASSAY, CARCINOGENESIS and TISSUE CULTURE # 349

COMMITTEE:
Dr. Kotin, Chm.
Dr. Jacobson
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TOBACCO INDUSTRY RESEARCH COMMITTEE
150 East Forty Second Street
New York 17, New York

APPLICATION FOR RESEARCH GRANT

DATE: April 18, 1962

1. Name of Investigator: ARTHUR FURST, PH.D.

2. Title: Director

3. Institution and Address: Institute of Chemical Biology
University of San Francisco
San Francisco 17, California

4. Project or Subject: "A CONTROLLED STUDY IS PROPOSED TO EVALUATE THE EFFECT OF ADMINISTRATION OF TRACE METALS (WITH OR WITHOUT EXPOSURE TO CIGARETTE SMOKE) ON THE INCIDENCE OF PULMONARY ADENOMAS IN STRAIN A MICE."

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5. Detailed Plan of Procedure:

Background to problem:

The highly inbred Strain A albino mice developed by Strong (J. Hered. 27, 21-24 (1926) is an excellent test animal for the study of primary tumors of the lung. The spontaneous incidence of these pulmonary tumors is well documented by Bittner (Pub. Health Rep. 54, 380-392 (1939) and Andervort (Pub. Health Rep. 52, 212-221 (1937) and J. Nat. Cancer Inst. 1, 225-239 (1940). Adequate statistical studies have also been published on these tumors.

Following some reports by Cogbill and Hobbs on the nickel content of cigarettes (Tobacco Sci. 1, 68-73 (1957), the Sundermans implicated nickel in tobacco as being carcinogenic. They reasoned that each cigarette contained 2 µg of Ni; the main stream smoke contains 2% to 7% CO. From these data they postulate that if Ni $(CO)_4$ can be formed, the amount inhaled by man would be three times that which is carcinogenic to rats (Am. J. Clin. Path. 35, 203-209 (1961).

The Proposal:

A study is proposed to evaluate the effect of nickel compounds on the incidence of spontaneous pulmonary adenomas in Strain A mice. Spectroscopically analyzed nickel (ous) acetate, or nickel chloride will be adminstered IP, or in the drinking water, or as an atomized spray to different groups of mice of

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same age and weight. Equal numbers of males and females will be used. The dosages will be calculated so that each group receives the same amount of nickel, and this value will be at least 100x reported found in cigarettes. Time of exposure will vary. One set of controls will get vehicle alone; a second set will get urethane solution. A third set of controls will get IP, or in the drinking water, a urethane-nickel complex solution. All dates will be analyzed statistically.

A method will be devised to analyze for nickel in lung tissue, both normal and malignant. The most sensitive reagent for nickel, 2, 3-quinoxalinedithiol, was developed at the University of San Francisco (Morrison and Furst, J. Org. Chem. 21, 470 (1956) and was adapted for inorganic quantitative analysis (Skoog, Lai and Furst, Anal. Chem. 30, 365 (1958).

The information obtained would help elucidate the role of nickel in the pathogenesis of lung tumors in Strain A mice.

Future:

After the first phase is completed in about one year, a conference would be requested with members of the Research Committee. If as a result of this discussion it is concluded that the study should be continued, the experiments would be repeated adding exposure to cigarette smoke as a new variable.

6. Budget Plan:

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| a. | Salaries | $5,000.00 |
| b. | Expendable Supplies (mice, chemicals) | 1,000.00 |
| c. | Permanent Equipment | -- |
| d. | Overhead (15% of a,b,e) | 960.00 |
| e. | Other (travel to meeting) | 400.00 |
| | TOTAL | $7,360.00 |

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7. Anticipated Duration of Work: First phase - One year
Second phase - Two additional years

8. Facilities and Staff Available: Complete facilities are available for study of the first phase. The Institute has the major equipment, including automatic spectrophotometers.

9. Additional Requirements: If second phase will be done, it will be necessary to acquire four smoking machines to be purchased from Mt. Zion Hospital (at $1,000) and a microscope. The addition of one diener will also be necessary. Total for the second year's budget will be $12,000, and $10,500 for the third year.

10. Additional information (including relation of work to other projects and other sources of supply)
A proposal has been submitted to the NIH for a study of the effect of trace metals on the carcinogenicity of azo dyes. These projects would complement each other.

Signature ARTHUR FURST
Director of Project

JAMES M. CORBETT, SEC'Y-TREAS.
Business Officer

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